REMARKS

Amendment

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Claim Objection

Claims 1, 24 and 27 were objected to for embracing two distinct inventions. The claims have been amended to recite the elected method of administering an immunogen.

The 35 U.S.C. §103(a) Rejection

Claims 1-8 and 24-29 were rejected under 35 U.S.C. §103(a) as being unpatentable over **Toida** et al. in view of **Rappuoli** et al., and further in view of **Schodel** et al. (Infect. Immunity, 1989; Vaccine 1990) and **Connell** et al. (Immuol. Lett., 1998; Infect. Immunity 1992). The rejection is respectfully traversed.

Applicants would like to first emphasize the differences between the present invention and the cited prior art. The present invention focuses on Type II enterotoxins (LT-IIa and LT-IIb), whereas Toida and others studied Type I enterotoxins. Although there is low nucleotide and amino acid homologies between the A polypeptides of Type I and Type II enterotoxins, there is no nucleotide or amino acid homologies for the B polypeptides. Type I and Type II enterotoxins also exhibit different ganglioside-binding activities. Therefore, in view of these significant structural and functional differences, one of ordinary skill in the art could not readily deduce immunomodulatory functions for one type of enterotoxin based on the properties of the other type without empirical experimentation.

The present invention is drawn to methods of inducing cellular immune responses by a recombinant immunogen comprising a fusion protein of an antigen fused to the A2 and B subunits of a type II heat-labile enterotoxin.

In contrast, **Toida** et al. teach a method of inducing immune responses using a chimeric immunogen comprising an antigen

fused to the A2 and B subunits of a Type I enterotoxin (cholera toxin). **Rappuoli** et al. teach the Type I enterotoxins *E. coli* heat labile enterotoxin and cholera toxin are potent mucosal immunogens. **Schodel** et al. teach a method of inducing immune responses using an attenuated *Salmonella* expressing a fusion protein consists of an antigen fused to the B subunit of the Type I enterotoxin *E. coli* heat labile enterotoxin. **Connell** et al. (1992) characterize hybrid toxins produced by assembly of A and B polypeptides from type I and type II heat labile enterotoxins. **Connell** et al. (1998) compare the adjuvant effect of cholera toxin and the Type II heat labile enterotoxin type IIa mixed with an antigen. **Connell** et al. (1998), however, only teach induction of antibody responses. **Connell** et al. (1998) do not teach or suggest induction of cellular immune responses by Type II enterotoxins as claimed herein.

Hence, the combined teaching only teaches a method of using a chimeric immunogen comprising subunits of a Type I enterotoxin such as cholera toxin. The combined teaching does not teach or suggest methods of inducing cellular immune responses by a chimeric immunogen comprising subunits of Type II entertoxin as claimed herein. Applicants submit that the combined teaching on

Type I enterotoxins would not render the instant invention of inducing cellular immune responses by Type II enterotoxins obvious. This is because (1) there are substantial structural and functional differences between Type I and Type II enterotoxin, and (2) there are fundamental biological differences between induction of antibody secretion and induction of cellular immune responses.

In summary, the combined teaching of the cited references does not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed methods. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 1-8 and 24-29 under 35 U.S.C. §103(a) be withdrawn.

Claims 1-8 and 24-29 were rejected under 35 U.S.C. §103(a) as being unpatentable over **Russell** et al. in view of **Rappuoli** et al., and further in view of **Schodel** et al. (Infect. Immunity, 1989; Vaccine 1990) and **Connell** et al. (Immuol. Lett., 1998; Infect. Immunity 1992). The rejection is respectfully traversed.

Russell et al. teach a method of inducing immune responses using a chimeric immunogen comprising an antigen fused to the subunits of a Type I enterotoxin (cholera toxin). The other cited references have been discussed above.

As discussed above, Applicants submit that the combined teaching of the cited references does not render the instant invention obvious. The combined teaching only teaches a method of using Type I enterotoxin. The combined teaching does not teach or suggest induction of cellular immune responses by Type II enterotoxins as claimed herein. Hence, the cited references do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed methods. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 1-8 and 24-29 under 35 U.S.C. §103(a) be withdrawn.

Double Patenting

Claims 1-3, 6-8, and 24-29 were rejected under the judicially created doctrine of obviousness-type double patenting as

being unpatentable over claims 1-9 of U.S. Patent 6,030,624, in view of **Rappuoli** et al., and further in view of **Schodel** et al. (Infect. Immunity, 1989; Vaccine 1990) and **Connell** et al. (Immuol. Lett., 1998; Infect. Immunity 1992). The rejection is respectfully traversed.

Claims 1-9 of U.S. Patent 6,030,624 are drawn to a method of using an attenuated bacteria expressing a chimeric immunogen consists of an antigen fused to the subunits of a Type I enterotoxin (cholera toxin). In contrast, the present invention is drawn to a method of inducing cellular immune responses by a immunogen comprising subunits of Type II enterotoxins.

As discussed above, Applicants submit that the combined teaching of the cited references does not render the instant invention obvious. Both claims 1-9 of U.S. Patent 6,030,624 and the cited references only teach a method of using Type I enterotoxin. The combined teaching does not teach or suggest induction of cellular immune responses by Type II enterotoxins as claimed herein. Applicants submit that the cited references do not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicants' claimed methods. The invention as

a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the double patenting rejection of claims 1-8 and 24-29 be withdrawn.

This is intended to be a complete response to the Office Action mailed August 26, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (amended) A method of inducing an immune response by administration of a recombinant immunogen comprising ~~expressed from a plasmid which comprises in operable linkage:~~

~~a) an origin of replication;~~

~~b) a promoter;~~

~~c) DNA sequence encoding~~ a fusion protein of an antigen ~~of interest~~ fused ~~in frame~~ to the A2 and B subunits of a type II heat-labile enterotoxin, wherein said immune response is selected from the group consisting of development of antigen-specific T cells in the circulation and tissues, the development of cytotoxic T cells and immunological tolerance to the antigen sequence. ~~; and~~

~~d) DNA sequence encoding subunit B of type II heat-labile enterotoxin for coexpression with the fusion protein of said antigen of interest to facilitate assembly of a chimeric protein.~~

Claim 24 has been amended as follows:

24. (amended) A method of increasing Th1 response and cell-mediated immunity by administration of a recombinant

immunogen comprising ~~expressed from a plasmid which comprises in operable linkage:~~

~~a) an origin of replication;~~

~~b) a promoter;~~

c) ~~DNA sequence encoding~~ a fusion protein of an antigen ~~of interest~~ fused ~~in frame~~ to the A2 and B subunits of a type II heat-labile enterotoxin; ~~and~~

~~d) DNA sequence encoding subunit B of type II heat-labile enterotoxin for coexpression with the fusion protein of said antigen of interest to facilitate assembly of a chimeric protein~~.

Claim 27 has been amended as follows:

27. (amended) A method of increasing Th1 response and cell-mediated immunity by administration of a recombinant immunogen comprising ~~expressed from a plasmid which comprises in operable linkage:~~

~~a) an origin of replication;~~

~~b) a promoter;~~

~~c) DNA sequence encoding~~ a fusion protein of an antigen ~~of interest~~ fused ~~in frame~~ to the A2 and B subunits of a *E. coli* heat-labile type IIa or type IIb toxin; ~~and~~

d) DNA sequence encoding subunit B of type II heat-labile enterotoxin for coexpression with the fusion protein of said antigen of interest to facilitate assembly of a chimeric protein.